IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Group Art Unit 1644

Diane J. Frauchiger
I, ~~Karen J. Jurkewski~~, hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Assistant Commissioner for Patents, Washington, D.C. 20231; on the date of my signature.

Diane J. Frauchiger
Signature

September 21, 2001
Date of Signature

In re

Patent Application of

Richard B. Mazess, et. al.

Serial No. 09/402,636

Filed: April 26, 2000

Examiner: Phillip Gambel, Ph.D.

"TARGETED THERAPEUTIC DELIVERY OF VITAMIN D COMPOUNDS"

DECLARATION UNDER 37 C.F.R. 1.132
OF JEFFREY W. DRISCOLL

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

I, Jeffrey W. Driscoll, Ph.D., declare and state the following:

1. I hold the position of Senior Chemist at Bone Care International, Inc., the assignee of the above-identified patent application.

2. I received a Bachelor of Science degree in Chemistry from the University of Wisconsin – Madison in 1983 and a Doctor of Philosophy degree in Chemistry from the University of North Carolina – Chapel Hill in 1993. I have worked in the field of chemistry at least as early as 1993 and in the field of pharmaceutical product synthesis and development at least as early as 1996. From 2000 to the present I have worked in the vitamin D area. My Curriculum Vitae is attached to this declaration and is incorporated herein by reference.

2. I am aware of the relative skill level of those in the art to which the invention disclosed and claimed in the above-identified application pertains. As of the filing date of the application, the ordinary level of skill in the art is a person having a doctorate degree or the equivalent in organic/pharmaceutical syntheses and having specific knowledge of vitamin D chemistry and biochemistry. Thus, the relative level of skill of chemists in the art is quite high. My experience is that of an expert in organic chemical and pharmaceutical synthetic techniques and analyses.

3. Prior to making this declaration, I was given a copy of U.S. Patent Application No. 09/402,636, entitled "Targeted Therapeutic Delivery of Vitamin D Analogues", filed in the U.S. Patent Office on April 26, 2000, claiming priority back to August 13, 1997. I have read and understood the subject application as filed, including the claims. I understand that only claims 1-7, 9, 11, 17, 18 and 20-22 are pending in the application. I have particularly reviewed independent claim 1, which recites a conjugate comprising at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest. I have also reviewed independent claim 20, which recites a pharmaceutical composition comprising a conjugate which includes at least one vitamin D moiety associated with at least one target molecule moiety having an affinity for a tissue of interest and a suitable pharmaceutically acceptable carrier.

4. At the same time, I was given a copy of the Office Action dated May 9, 2001. I have reviewed the Office Action and all the references cited by the Examiner, especially the Examiner's assertion that while the specification of the patent application enabled conjugates of vitamin D wherein the vitamin D moiety is linked to various bisphosphonate moieties via an amide linkage, the specification is insufficient with

respect to linkage of the vitamin D moiety to estrogens and their estrogen equivalents and anti-estrogens. Specifically, the Examiner alleges that there is insufficient biochemical information regarding the chemical reaction, the condition to which the reaction will take place, the functional group with the estrogen, antiestrogen and estrogen equivalent structure may be suitable for linking to vitamin D. Thus, the Examiner concludes that predicting which estrogen or antiestrogen will conjugate with vitamin D under unspecified conditions is complex and requires undue experimentation to practice the claimed invention.

5. Based on my experience and my review of the application and the Office Action, I state that the specification of the present applications provides the required guidance and direction to the skilled chemist in the relevant art so that such a chemist would have understood the meaning and breadth of the different claimed conjugates that comprise at least one vitamin D moiety associated with a target molecule moiety having an affinity for a tissue of interest as well as pharmaceutical compositions comprising the same. More particularly, one of ordinary skill would have known how to conjugate target molecule moieties having affinities for a tissue of interest to appropriate vitamin D moieties based on the disclosure. Even more particularly, one having ordinary skill in the art would have known how to select appropriate estrogen or estrogen equivalents as target molecules, bone-targeting molecules, or therapeutic agents. Further, the skilled chemist would have known how to select appropriate connecting groups in order to associate appropriate target molecule moieties with the vitamin D moieties. In my opinion, the disclosure in the present application provides sufficient information to make and use the invention, and making and using the invention would not require undue

experimentation by one of ordinary skill. I have come to this conclusion for the following reasons:

(i) According to the specification of the patent application, the invention described and claimed in the application involves conjugates having at least one vitamin D (designated as "D") moiety associated with at least one target molecule moiety (designated as "T") are represented by formula (I): $D_{(m)}*(T)_n$, wherein n and m represent integers of 1 or greater and * indicates an association between D and T. It is clear from the specification that D represents "at least one vitamin D compound, analog, component or moiety" (page 10, lines 14-15); T represents "at least one target molecule moiety"; and "n and m represent integers of 1 or greater" (page 10, line 17). The specification discloses that it may be desirable to "conjugate hormones or other agents (designated as "A") to the conjugates of formula (I), to form a bifunctional conjugate represented by formula (XV) $(D)_m * (T)_n * (A)_p$, wherein A represents a therapeutic agent other than vitamin D and p is an integer of 1 or greater, D, T, m and n are as previously defined herein, with the proviso that D and A maintain their biological effectiveness" (page 22, lines 3-11). The specification indicates that "a bifunctional conjugate of formula (XV) is one that has the ability to deliver vitamin D to bone as well as another osteogenic agent such as an estrogen" (page 22, lines 11-13).

(ii) More particularly, "D" or "'vitamin D' includes all compounds having the conventional vitamin D structure of A, C and D

rings and C-17 side chain as well as previtamin D compounds which are the thermal isomers of their corresponding vitamin D forms, in which the basic structures may be substituted, unsubstituted, or modified" (page 10, lines 21-25). The term "target molecule" or "targeting molecule" "refers to a molecule that binds to or influences metabolism or the tissue of interest" (page 9, lines 12-14). "For example, bone-targeting agents may include bone-seeking molecules such as tetracycline, calcitonin, bisphosphonates, chelators, phosphates, polyaspartic acid, polyglutamic acid, ...: estrogens and other steroids such as dehydroepiandrosterone (DHEA)" (page 9, lines 14-22).

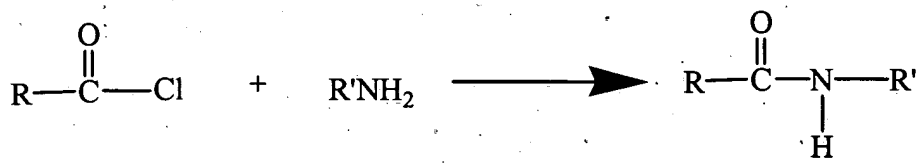
(iii) The terms "associated with" or "association" are clearly defined in the specification: these terms refer to "attachment of linkage of one component of the conjugate (e.g. the vitamin D moiety) or vitamin D moiety and connector to another component of the conjugate, e.g., the target molecule or target molecule and connector, via covalent bonding, hydrogen bonding, metallic bonding, van der Waal forces, ionic bonding, coulombic forces, hydrophobic or hydrophilic forces, adsorption or absorption, chelate type association, or any combination thereof" (page 10, line 30 to page 11, line 4).

(iv) The specification further indicates that included within the scope of the present invention are conjugates of formula (XV) which are bone-therapeutic conjugates wherein A is a hormone or other agent which is known to ameliorate bone diseases or disorders. "The term "bone-

therapeutic agent" is used ... to refer to a specific type of therapeutic agent, one which ameliorates bone diseases or disorders when delivered or administered to bone." (page 10, lines 5-9). "Such bone agents may include conjugated estrogens or their equivalents, antiestrogens, calcitonin, bisphosphonates, calcium supplements cobalamin, pertussis toxin, boron, DHEA and other bone growth factors such as transforming growth factor beta, action or bone morphonogenic protein" (page 22, lines 14-21).

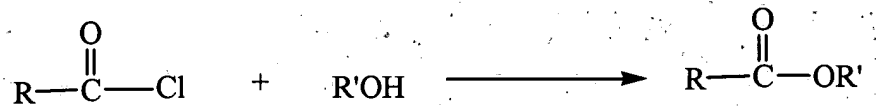
(iv) The specification provides several examples of synthetic schema wherein bone-therapeutic agents, specifically bisphosphonates, are conjugated to a vitamin D moiety. The first step in all of these schema is the reaction of an unprotected hydroxyl group of the vitamin D compound with phosgene, C=COCl, to form an acyl halide group on the vitamin D compound, e.g., product 2 of the reaction scheme of Figure 1. Acyl halide groups are well known in the art as being very reactive functional groups, and reaction with amines and hydroxyls (i.e., alcohol groups) are some of the most well known organic synthetic reactions.

The acylation of amines by acyl halides yields amides or an amide linkage. This general reaction, exemplifying acyl chlorides, is shown as follows:



As seen in Figure 1 of the specification, the formation of an amide linkage is shown in the reaction of 2 with 3, a bisphosphonate with an amino group, to form an amide linkage, illustrating again the well-known amide formation reaction.

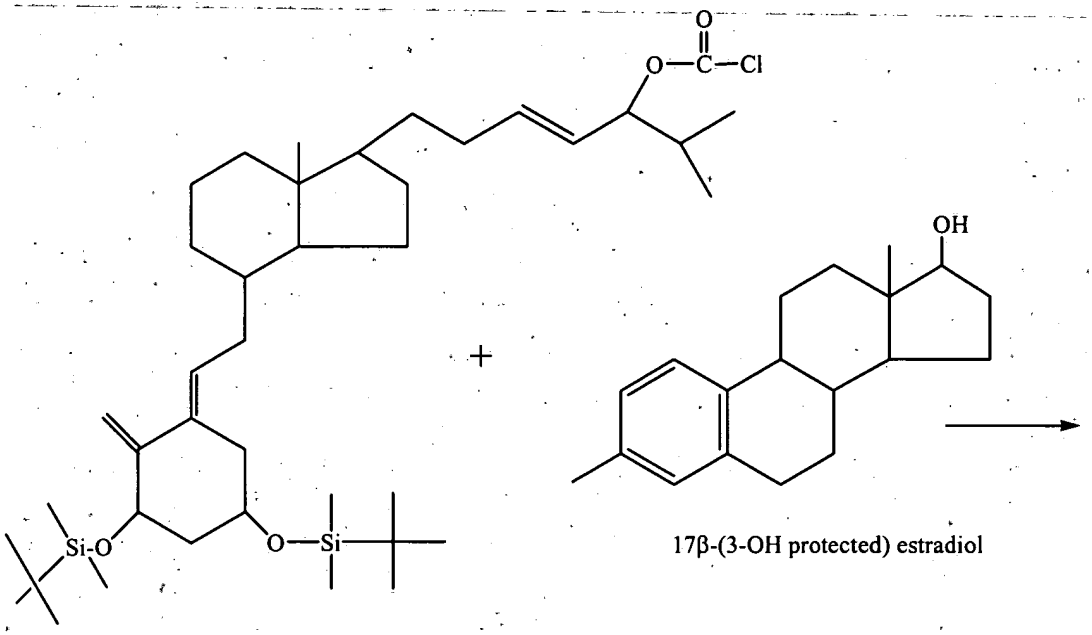
The reaction of acyl halide groups with hydroxyl groups yields carboxylic esters or an ester linkage. This general reaction is shown as follows:



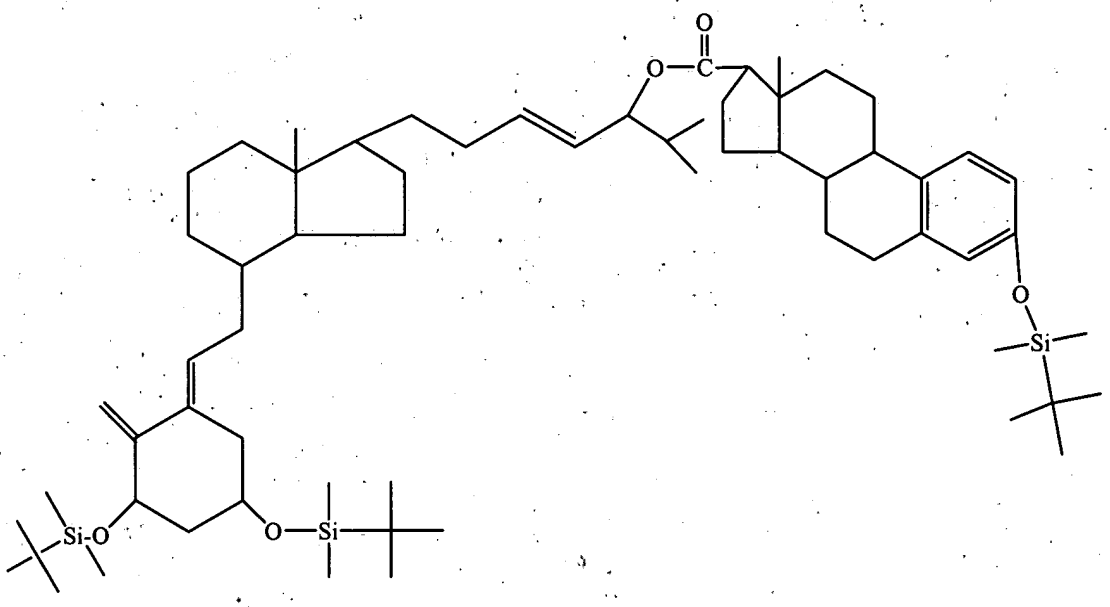
In fact, the alcholysis of acyl halides, i.e., the reaction between acyl halides and alcohols, is one of the best general methods for the preparation of esters. (See, pages 346 and 370, J. March, Advanced Organic Chemistry, John Wiley & Sons (1985), copy attached hereto.)

The latter reaction is particularly pertinent to the formation conjugates of vitamin D (the vitamin D having a highly reactive acyl halide, e.g., acyl chloride, group) with the hydroxyl groups of, e.g., estrogens. A common estrogen is 17β-estradiol, a compound that has 2 hydroxyl groups. Either of these hydroxyl groups could react with the acyl chloride of, e.g., vitamin D acyl chloride (product 2), to form a ester linkage, and thus a vitamin D-estrogen conjugate. (It is noted that an unreacted hydroxyl group or any other functional group that would react with the acyl chloride would have a protecting group as shown in the

reaction below.) The reaction of 17β-estradiol as the estrogen and product 2 as the vitamin D reactant is shown below:



17β-(3-OH protected) estradiol



Using the guidance of the bisphosphonate conjugate synthetic schema and knowledge of these general reactions well known in the art, one of ordinary skill in the art would have known how to conjugate a vitamin D moiety with an estrogen, estrogen equivalent or the other disclosed target molecules to form the claimed conjugates and pharmaceutical compositions as of the filing date of the present application. In other words, to make the claimed conjugates and compositions, the specification describes known synthetic techniques. These conjugation techniques, e.g., the formation of an amide linkage or an ester linkage using acyl halide groups, have been known for decades.

6. The claimed invention relies on synthetic technologies known at the time of the filing date of this application. The description of the invention is of sufficient detail and comprehensiveness that chemists knowledgeable in the required field could have made the conjugates and pharmaceutical compositions of the invention as of the date of the filing of the patent application. As a result, it is my opinion that one of ordinary skill in the art would have understood from the syntheses of bisphosphonate conjugates and related references that vitamin D can be linked with any of the target molecules that have an amine or a hydroxyl group.

7. In conclusion, from reading the specification alone, or combining the disclosure therein with what was generally known in the art at the time the application was filed, I believe sufficient biochemical information relating to the chemical reactions, the condition by which the reactions take place, and the functional groups that provide suitable linkage between estrogen, antiestrogen, estrogen equivalent structures and other

target molecules to vitamin D was provided in, or could be easily extrapolated from, the specification so that the skilled chemist could practice the claimed invention. Moreover, I believe that no undue experimentation would be required by one of ordinary skill in the art to determine which estrogen, anti-estrogens or target molecules will conjugate with vitamin D.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statement may jeopardize the validity of the application or any patent issued thereon.

Date: Sept. 6, 2001

Jeffrey W. Driscoll, Ph.D.

Jeffrey W. Driscoll
7430 Meadowrue Circle
Middleton, WI 53562

Summary: 18 years post-baccalaureate experience in research, management and education. Experience in physical, analytical and organic chemistry within the chemical and pharmaceutical communities. Thorough understanding or cGMP regulations. Excellent teamwork, multitasking and communication skills.

Work Experience:

Bone Care International
Senior Chemist — September, 2000 – Present

- Developed analytical assays in support of preclinical development
- Streamlined departmental operations by organizing equipment and consumables into a computer based system
- Designed and implemented experiments in support of patent work
- Provided company wide support with OSHA regulations as a member of the Safety Committee
- Designed and executed experiments in support of FDA requirements of company's final product

Custom Synthesis Services
Senior Scientist — May 1998 to September 2000

- Designed and implemented multi-step organic syntheses of active drugs and metabolites for the pharmaceutical industry
- Organized the company's synthetic database into a computer based system
- Trained personnel in the procedures and mechanics of successfully searching Beilstein and the Chemical Abstracts systems for chemical information

Wisconsin Analytical and Research Services /Pharmaceutical Product Development
Scientist, Analytical Reference Standards and Controlled Substances — January 1996 to May 1998

- Responsible for Analytical Reference Standards Program for Bioanalytical and Product Analysis Division
- Responsible for managing outside sourcing of standards from custom synthesis labs, including negotiating contracts and tracking orders to delivery
- Member of the Safety Committee

Aldrich Chemical Company
Quality Control Scientist — September 1993 to November 1995

- Responsible for release of products by review of analytical data in the Quality Control laboratories
- Developed HPLC methods for the separations of stereoisomers
- Developed methods for process control of deuteration experiments using on-line IR spectroscopy
- Member of the Safety Committee

Education: **University of North Car lina at Chapel Hill**
Ph.D., Chemistry, 1993
M.Sc., Chemistry, 1990

University of Wisconsin-Madison
B.S., Chemistry, 1983

Other Affiliations

United States Naval Officer, 1983 to 1988
American Chemical Society
American Association of Pharmaceutical Scientists
Adjunct Professor of Chemistry, Edgewood College